THE BULLETIN OF
Mathematical
BIOPHYSICS

THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 4
NUMBER 2
JUNE 1942

THE BULLETIN OF
Mathematical Biophysics
EDITED BY N. RASHEVSKY

The Bulletin is devoted to publications of research in Mathematical Biophysics, as described on the inside back cover.

THE BULLETIN is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $2.50 per year, the price of single copies is 75 cents. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to The University of Chicago Press in postal or express money orders or bank drafts.

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BUSINESS CORRESPONDENCE should be addressed to The University of Chicago Press, Chicago, Ill.

COMMUNICATIONS FOR THE EDITOR and manuscripts should be addressed to N. RASHEVSKY, Editorial Office of the Bulletin of Mathematical Biophysics, 5822 Drexel Avenue, Chicago, Ill.

PRINTED BY THE DENTAN PRINTING CO., COLORADO SPRINGS, COLORADO

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Mathematical Biophysics

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VOLUME FOUR JUNE 1942 NUMBER TWO

IMPORTANT ANNOUNCEMENT

The increase in the output of papers in the field of mathematical biophysics makes it difficult to insure prompt publication without an increase in the size of the journal. Therefore, the Bulletin of Mathematical Biophysics inaugurates the following service:

Upon acceptance of a paper, the Editor, if necessary, will ask the author to shorten the paper to an extent dictated by the requirements of a reasonably prompt publication. The shortening should in no case reduce the paper to a mere abstract. Such a shortened paper will be published within six months or less.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

A MATHEMATICAL ANALYSIS OF ELONGATION AND CONSTRICTION IN CELL DIVISION

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An equation for the rate of elongation of a dividing egg is integrated and generalized. The rates of elongation and constriction of a number of eggs under various conditions are analyzed and compared with the theoretical predictions. The theory accounts rather well for a large body of data on elongation and constriction. The general shapes of the elongation and constriction curves are predicted and the orders of magnitude of the parameters are satisfactory. One of the parameters for the elongation curves is related theoretically to the parameter of the constriction curves, and the correct order of magnitude is obtained if one parameter is predicted from the other.

The factors involved in cytokinesis are many and varied and the influence of various chemicals and physical changes on the process have been studied extensively. Several theories have been advanced as to the source of the mechanical forces involved in the process of deforming the cell (cf. Wilson, 1925). Included in these hypotheses are such factors as changes in form of the astral figure (Chambers, 1924; Gray, 1931), production of a coagulating principle (Burrows, 1927), variation in surface forces over the cell surface (Spek, 1918), forces of an electrical nature, changes in permeability (Lillie, 1918), changes in viscosity due to sol-gel transformations (Chambers, 1938; Marsland, 1939), equatorial intrusion and polar pseudopodial movements (Schechtman, 1937), osmotic forces and drag forces due to diffusion of metabolites (Rashevsky, 1938).

It is possible to divide oil drops by reducing the oil—water tension on two sides with a resulting elongation in the direction of minimum tension (Spek, 1918; Wilson, 1925). The possible effect of surface forces varying axially has been considered theoretically by G. Young (1939a) for the case of a true surface tension with a variation of the tension along the surface. Depending on how the tangential stress is sustained, one can obtain either shortening or elongation for a given case. The effect of surface forces will be discussed in greater detail subsequently. Calculations by N. Rashevsky (1938) and R. Williamson (1939) indicate that the effect of electrical forces would be small compared to those of diffusion. In the above mentioned hy-

potheses, except the last, little attempt has been made to predict any quantitative changes or to develop any mathematical theory of the effect of the various factors. Just how the forces arise is not clear in most cases. This in no way invalidates them, but makes difficult a mathematical treatment of the theories, at least until some investigation is made concerning the manner in which the forces arise. However, a considerable number of facts can be brought together with their aid. Theoretical investigation along these lines is definitely suggested. In the present paper we shall limit our discussion to the case in which only diffusion forces, osmotic forces and surface tension act, and in which viscosity opposes motion.

The nature of diffusion drag forces has been discussed in a number of papers (Rashevsky, 1938; Young, 1938; Landahl, 1942). As part of a program to investigate theoretically possible factors involved in cell division, this type of force has been considered (Rashevsky, 1938; Young, 1939), and certain predictions regarding elongation and constriction have been obtained. It is our purpose to extend some of these results, compare the predictions with experimental data, and to discuss the implications of the restrictions thus imposed on the parameters.

A COMPARISON OF THE ELONGATION EQUATION WITH EXPERIMENTAL DATA

An equation for the elongation of freely dividing cells as a function of time. We start with the expression for the rate of elongation given by N. Rashevsky (1940, chap. iii, eq. 44):

$$\frac{r_1}{r_1 - r_2}\frac{dr_1}{dt} = \frac{K}{1 + \frac{1}{2}(1+b)\frac{r_0^3}{r_1^3} + b\frac{r_0^{3/2}}{r_1^{3/2}}} - \frac{\gamma r_1^{3/2}}{2\eta r_0^{3/2}}, \tag{1}$$

where

$$K = \frac{RTq\mu r_0^3}{4M\eta D_e} \tag{2}$$

and

$$b = \frac{2D_i}{D_e}. \tag{3}$$

The parameters $2r_1$ and $2r_2$ are the length and width of a cell whose diameter is $2r_0$ in the spherical shape; γ is the surface tension, η the viscosity of the interior of the cell, t the time, D_e and D_i the effective external and internal diffusion coefficients, q the effective rate of production of metabolites of average molecular weight M, μ the

fractional volume of non-solvent particles on which the diffusion forces act, T the temperature and R the gas constant (Rashevsky, 1940). In view of subsequent work (Landahl, 1942), the expression for K is actually more complex than given by (2), but about of the same order of magnitude.

Equation (1) is not expected to hold for too great elongations. Thus let

$$\varepsilon = (r_1 - r_0)/r_0 . \tag{4}$$

The volume is practically constant, and is given by

$$V = \frac{4}{3}\pi r_1 r_2^2 = \frac{4}{3}\pi r_0^3 . \tag{5}$$

From (4) and (5) we have r_1 and r_2 in terms of ε. Introducing these values into (1), expanding and retaining only the first three terms of the expansions, and rearranging, we obtain

$$\frac{d\varepsilon}{dt} = A\varepsilon - B\varepsilon^2 - C\varepsilon^3 , \tag{6}$$

where

$$A = \frac{1}{r_0}\left[\frac{K}{(1+b)} - \frac{3\gamma}{4\eta}\right], \tag{7}$$

$$B = \frac{1}{4r_0}\left[\frac{K}{(1+b)^2}(1-3b) + \frac{3}{4}\frac{\gamma}{\eta}\right], \tag{8}$$

$$C = \frac{1}{24r_0}\left[\frac{K}{(1+b)^3}(19+50b+7b^2) - \frac{3}{4}\frac{\gamma}{\eta}\right]. \tag{9}$$

Integrating (7) and solving for t, we obtain

$$t = t_0 + \frac{1}{2A}\log\frac{\varepsilon^2}{A - B\varepsilon - C\varepsilon^2} + \frac{B}{2A\sqrt{B^2+4AC}}\log\frac{\sqrt{B^2+4AC}+B+2C\varepsilon}{\sqrt{B^2+4AC}-B-2C\varepsilon} \tag{10}$$

Starting with a more complete equation (Rashevsky, 1940, chap. iii, eq. 14) including the permeability, h, so that osmotic forces are taken into account, we obtain as above an expression of the form (10). The parameters corresponding to A, B and C are now rather complex, and are of the form

$$A' = \frac{1}{r_0}\left[K' - \frac{3\gamma}{4\eta}\right], \tag{11}$$

$$B' = \frac{1}{4r_0}\left[G_1 K' + \frac{3\gamma}{4\eta}\right], \tag{12}$$

$$C' = \frac{1}{24r_0}\left[G_2 K' - \frac{3\gamma}{4\eta}\right], \tag{13}$$

where

$$K' = \frac{RTqr_0^3}{12M\eta}\,\frac{3\mu r_0 h - D_e(2-3\mu)}{2D_i D_e + r_0 h(2D_i + D_e)}, \tag{14}$$

and the factors G_1 and G_2 depend upon the value of b as defined above, as well as upon the extent to which $3r_0h$ exceeds $D_e(2 - 3\mu)$. The actual expressions for G_1 and G_2 are very complex and so are not given here.

As μ would not exceed about one-third, and is probably not less than one-twentieth, the requirements that the $K' > 0$ is that r_0h be larger than D_e by a factor from $\frac{1}{2}$ to 10 depending on μ. If $r_0h > D_e$, it follows from the expression for Λ, the total diffusion resistance of a spherical cell (Rashevsky, 1940, chap. i, eq. 21 and 23), that the contribution to the resistance due to the external medium is greater than that due to the plasma membrane. This is not so for relatively impermeable substances and in particular is not so for oxygen if one uses the known values of D_e, r_0 and the estimated value for h (Landahl, 1937; Rashevsky, 1940, chap. ii) for eggs with outer membranes. However, the permeability without the outer membrane may be considerably larger. If it is larger by a factor of about ten, then we would have $r_0h > D_e$. For many metabolites not enough information is known and thus we cannot arrive at any conclusions. The restriction is an important one, and must be considered in greater detail eventually, but we shall not do so here. If $r_0h < D_e$, but if $q < 0$, division is still possible for certain cell sizes. This case has been discussed by N. Rashevsky (1940, chap. iii).

The effect of the variation of production rate with concentration on the elongation equation. In the development of the elongation equation, it has been assumed that q was essentially a constant. We may inquire as to the effect of a q which depends upon the concentration. One might wish to consider the case in which the production, q, is proportional to the average concentration, or the case in which there is a constant production but a resynthesis going on proportional to the concentration. These cases can be summarized in the expression

$$q = q_0 + a\bar{c} \,. \tag{15}$$

For the first mentioned case $q_0 = 0$, while for the second case $a < 0$.

Using the approximation method (Rashevsky, 1940), we may derive the expression for elongation. The expression is cumbersome, but if we proceed as above, we may obtain an expression for the rate as a parabola (see next section) in which instead of A we use the expression A' given by

$$A' = A\left[1 + \frac{ar_0^2(1+b)}{9D_i}\right] \tag{16}$$

and instead of B the expression B' given by

$$B' = B\left[1 + \frac{ar_0^2(1+b)}{9D_i} + \frac{ar_0^2 A}{9D_e B}\right] . \tag{17}$$

A and B are again given by (7) and (8) but instead of q in K of equation (2) we write $q_0 + ac_0$, where c_0 is the external concentration. The third term in the brackets of (17) is less than the second, since $D_e > D_i$ and $B > A$. Thus, A' and B' differ from A and B by the factor in the brackets of (16). As $q = q_0 + ac_0$, $a < q/c_0$ for $a > 0$. For *Arbacia* eggs the factor may be written approximately as one plus a quantity of the order of, or less than, $q/(bc_0)$. Unless b and c_0 are taken to be smaller than would ordinarily be expected, this latter term is smaller than one, and A' and B' are approximately the same as A and B respectively. On the other hand, if the value of $q/(bc_0)$ is larger than one, A and B would be changed by about the same amount. If this term is considerably greater than one, the approximation method breaks down seriously. One could perhaps allow for a factor of the order of ten.

If a is negative, A' and B' may be reduced in magnitude. If the factor $q/(bc_0)$ is small, we may disregard it and we may drop the primes. If the factor approaches unity, then A' may be appreciably less than A, and B' might become negative. This is a rather special case. If the factor exceeds unity, A' is negative. But we are only interested in A' greater than zero, since this is the case for dividing eggs.

From the above results, we see that the difference between a constant rate of production, q, and a q proportional to concentration or a q which increases or decreases linearly with concentration, is slight as far as its effect on the slope of the elongation curve is concerned. The parameters may be changed by a fairly large factor, but the ratio of A to B will probably not be affected appreciably.

The effect on the elongation curve of a force proportional to the gradient of the concentration compared with that due to the gradient of the logarithm of the concentration. In a previous paper (1942) it was seen that the force might be proportional to the gradient of the logarithm of the concentration $c = mN$, rather than to gradient c. The result is that, if the force is derived from a potential, the latter is proportional to log c. It is the difference in potentials at the "ends" and "sides", log c_1 − log c_2, that enters into the elongation equation (Rashevsky, 1940, p. 43, for $h = \infty$). But this is log (c_1/c_2). Only small differences of concentration are required to produce a considerable effect. Thus, c_1 is of the order of c_2 and hence log (c_1/c_2), which is equal to log $[1 + (c_1 - c_2)/c_2]$, is approximately $(c_1 - c_2)/c_2$. Since the difference $c_1 - c_2$ varies much more than c_2, we may treat c_2 as a constant for a first approximation. We then have the same result that would be obtained if the force were proportional to gradient c. Thus whether the force is proportional to gradient c or to gradient log c, the resulting expression for elongation is the same to a first approximation.

A general comparison of the equation of elongation with experimental data. Timed photographs of dividing *Arbacia* eggs during divison were made by R. Buchsbaum and R. Williamson (1942) for the purpose of testing some of the theoretical conclusions which follow from the diffusion drag force hypothesis. Some measurements of elongation of *Arbacia* eggs are given by L. Churney (1936, 1940), but no constriction measurements were made simultaneously as would be necessary for our discussion. We shall confine our considerations to the data first mentioned. In most cases the eggs were denuded of the fertilization membranes. These cells without membranes elongate markedly during the process, taking on a dumb-bell shape. It is this process of elongation which we are considering. After elongation ceases, the egg slowly shortens to some extent. For the present this effect will not be considered.

The rate of change of the relative elongation with time is given by equation (6). The parameter A must be positive. A negative A would correspond to a case in which a cell became shortened before beginning to elongate. Since this is not observed, A must be positive. Then for $A > 0$, it follows that $C > 0$. The parameter B is positive if $b \leqq 1/3$, and negative if $b \geqq 1$. It changes sign at some point in this interval depending on the values of A and K. If $B = 0$ and $C > B$, we may ignore the last term and the expression is a parabola. On the other hand if B should be very much smaller than C we may drop that term and we have the rate given by the linear and cubic

terms. If B and C must both be taken into account, one will generally have a curve whose shape is intermediate. If one normalizes the expression so that the maximum value of the rate, ε'_m, is unity, and the value of ε, ε_m, at which ε' returns to zero is also unity, then the shapes of the curves may be readily compared. Designating the normalized variables as ε'^* and ε^*, the expressions corresponding to $B = 0$ and $C = 0$ are respectively

$$\varepsilon'^* = \frac{3\sqrt{3}}{2}\varepsilon^*(1 - \varepsilon^{*2}), \tag{18}$$

$$\varepsilon'^* = 4\varepsilon^*(1 - \varepsilon^*). \tag{19}$$

These expressions have no arbitrary parameters and enable us therefore to compare data obtained on different cells. Thus, if the curves for these expressions are graphed, one should expect that any experimental data, to which they are to be compared, should lie between them if there were no error of measurement. In Figure 1, these

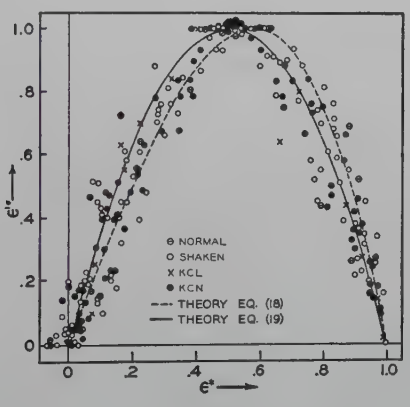

FIGURE 1

expressions are graphed, the former expression being shown as a broken line, the latter as a solid curve. To test this expectation, the measurements of the slopes of the elongation curves were made from each of thirty-four eggs under various conditions. These values were normalized in the sense used above and plotted in Figure 1. A discussion of the specific cases will be given later. The various symbols used to represent the measurements are explained in the figure. For each curve, the slopes were determined at about six to ten points. The scatter in the measurements is rather large as may be expected from measurements of slopes. However, within the range of error, it is clear that the average trend of the data lies approximately within the range of

the theoretical curves. The absence of arbitrary parameters in the theoretical curves increases the significance of the agreement. To the extent of the agreement we may say that the form of the experimental curve is predicted correctly by the theory.

It will be noted that the data scatter about the origin. The origin is determined in each case by the initial radius r_0 as determined by proper average of several measurements of cell diameters prior to appreciable elongation. Some cells appear slightly elongated for some time prior to beginning of elongation for division while others are slightly compressed. A few showed a slight shortening before beginning to elongate. This may be due in part to changing in position of the cells as discussed by L. Churney (1936). If this is the case, the variation caused should be randomly distributed, and one would still be justified in using the initial trend. This effect is only appreciable near the origin. It should also be pointed out that the approximations made in deriving the original expression (1) begin to break down at about the maximum of the curve. Without a more detailed investigation, one cannot expect agreement in the latter part of the curve, but it may be considered as an extrapolation.

The fact that a parabola is a fairly good approximation to the experimental curve as shown in Figure 1 suggests that one might use only the first two terms of (6). This could be done only if the values of the parameters are not significantly altered. If one first assumes C to be zero, and determines A and B from a comparison with the experimental curve, the parameters K and γ/η are obtained from equation (7) and (8). Similarly one can obtain these parameters by assuming $B = 0$. It is found that essentially the same values are found for K and γ/η in each case. The value of K obtained in the second case varies only by a factor 4 when b varies from 0 to 2, while γ/η varies less than about 1/2, unless b becomes large enough to make B negative when this can occur. But then C must necessarily play the dominant role and we thus obtain essentially the same values for K and γ/η, unless B takes on so large a negative value that a much larger value is obtained for C from the complete expression than would be the case when B is set equal to zero. We shall thus for simplicity drop the $C\varepsilon^3$ term as well as b in most of the further discussions. Instead of equation (10) we have

$$\varepsilon = A/(B + Ae^{-A(t-t_0)}), \tag{20}$$

where t_0 is an integration constant. A and B are given by expressions (7) and (8) so that we have, solving for K and γ/η,

$$K = r_0(A + 4B)/2, \tag{21}$$

$$\gamma/\eta = 2r_0(4B - A)/3 . \qquad (22)$$

Eggs with membranes. In the process of division, eggs with membranes elongate about twelve per cent (cf. Churney, 1936). The membrane appears to act only as a restraining sac which is elastic, and can be considered as outside the cell proper. One should then probably replace the surface tension γ by a more complex expression. We shall, however, evaluate the parameters on the basis of the same equation.

The curves of elongation of five eggs at first cleavage with fertilization membranes intact were plotted and the parameters A and B determined. One of these eggs had been treated in 10^{-4}M KCN for twenty minutes and had been shaken. A second egg had also been shaken. The relative error is large because the amount of elongation is small, but the ranges of values for A and B were not large. The parameters A and B as well as the time from fertilization to first division from the KCN treated egg did not take on values outside of the range of the other eggs. The average value of A for the other eggs was 0.025 ± 5 sec.$^{-1}$ while the value of B was 0.22 ± 3 sec. $^{-1}$. No values varied by more than fifty per cent of these averages. From these values, we find $K = 1.7 \times 10^{-3}$ cm. sec.$^{-1}$ and $\gamma/\eta = 2.1 \times 10^{-3}$ cm. sec.$^{-1}$. Further discussion of these values will be made subsequently. The average value of maximum elongation, ε_m, was $\varepsilon_m = .12 \pm 1$, while the average of the maximum slope, $(d\varepsilon/dt)_m = \varepsilon'_m$, was $\varepsilon'_m = 3.7 \pm 9 \times 10^{-4}$ sec^{-1}. The average value of the time from fertilization to beginning of division t'_0, as measured by the intercept of the line of maximum slope with the line $\varepsilon = 0$, was found to be $t'_0 = 48 \pm 3$ min. The value t'_0 is more easily determined than t_0 of equation (20), and is about two minutes less than the latter, the latter being approximately the time to the inflection point. The average initial diameter was $2r_0 = 74 \pm 2 \times 10^{-4}$ cm. The number after the $\pm$ sign in each case gives the mean variation about the average. In this case it was estimated on the basis of values from the five eggs.

Eggs with membranes removed by shaking. Sixteen elongation curves of eggs with the fertilization membranes removed by shaking were selected as being suitable to compare with the theoretical equation (20). The parameters were thus found to have the values $A = 0.024 \pm 4$ sec.$^{-1}$ and $B = 0.059 \pm 9$ sec.$^{-1}$. From these values we obtain $K = 4.5 \times 10^{-4}$ cm. sec.$^{-1}$ and $\gamma/\eta = 4.9 \times 10^{-4}$ cm. sec.$^{-1}$. Other average values are: $\varepsilon_m = .40 \pm 5$, $\varepsilon'_m = 2.3 \pm 3 \times 10^{-3}$ sec.$^{-1}$, $t'_0 = 46 \pm 4$ min., $2r_0 = 69.5 \pm 15 \times 10^{-4}$ cm. Comparing these values with those from eggs with membranes, we see that not only the extent of elongation is greater without membranes, but the maximum rate is

about six times as large. The values t'_0 and r_0 are essentially the same, as is also the parameter A. But B is much smaller, so that K and γ/η are both smaller, especially γ/η. A sample curve is shown in Figure 2*a*. The curve of constriction will be discussed later. In this

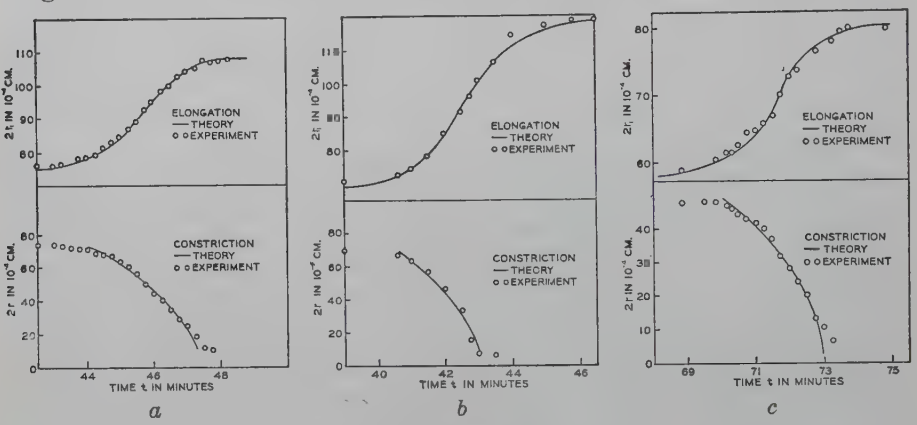

FIGURE 2

case there are more points than there are for most curves. The parameters are $A = .029$ sec.$^{-1}$, $B = .069$ sec.$^{-1}$, $t_0 = 46.1$ min., and $2r_0 = 75.5 \times 10^{-4}$ cm. This value is obtained by extrapolating the slope curve to zero and is two per cent higher than that obtained by averaging several diameters.

Eggs with membranes removed by KCl treatment. Two elongation curves from eggs with membranes removed by treatment with KCl were used to obtain the various parameters. The eggs did not show any hyaline material on the surface. The values of the parameters are: $A = .019$ sec.$^{-1}$, $B = .032$ sec.$^{-1}$, $\varepsilon_m = .58$, $\varepsilon'_m = 2.7 \times 10^{-3}$ sec.$^{-1}$, $t'_0 = 44.7$ min., $2r_0 = 73.0 \times 10^{-4}$ cm., and $A = .021$ sec.$^{-1}$, $B = .029$ sec.$^{-1}$, $\varepsilon_m = 71$, $\varepsilon'_m = 4 \times 10^{-3}$ sec.$^{-1}$, $t'_0 = 40.8$ min., $2r_0 = 69.2 \times 10^{-4}$ cm., giving the average values $K = 2.6 \times 10^{-4}$ cm. sec.$^{-1}$ and $\gamma/\eta = 2.4 \times 10^{-4}$ cm. sec.$^{-1}$. The latter curve is shown in Figure 2*b*, where $t_0 = 42.9$ min. Comparing with the values from eggs with membranes removed by shaking, we find that the extent of elongation is significantly increased, that the maximum rate probably increased, that A remained essentially unchanged, and B decreased about one-half, so that K and γ/η decreased, especially the latter.

Eggs with membranes removed by shaking and treated with KCN. Twelve elongation curves from eggs without membranes and treated with KCN were used to determine various parameters. There is some variation in both the concentration of KCN and time of treatment, but we shall treat the group as a whole. In most cases, the

concentration was between 10^{-4} and 10^{-5} M and the eggs remained in the solution from a short time after insemination. The average values of the various parameters obtained are: $A = .020 \pm 3$ sec.$^{-1}$, $B = .048 \pm 9$ sec.$^{-1}$, $\varepsilon_m = .44 \pm 2$, $\varepsilon'_m = 2.2 \pm 4 \times 10^{-3}$ sec.$^{-1}$, $t'_0 = 57 \pm 7$ min., $2r_0 = 68.4 \pm 7 \times 10^{-4}$ cm., $K = 3.6 \times 10^{-4}$ cm. sec.$^{-1}$, and $\gamma/\eta = 3.9 \times 10^{-4}$ cm. sec.$^{-1}$. Comparing these values with those from eggs treated the same but without KCN we find that the effect of the KCN is noticeable in the increase in t'_0. The other differences are not at all significant.

Eggs with membranes removed by shaking, second cleavage. Three cells with membranes removed by shaking were followed into second cleavage. From six curves, the following values were found: $A = .025 \pm 3$ sec.$^{-1}$, $B = .071 \pm 12$ sec.$^{-1}$, $\varepsilon_m = .35 \pm 2$, $\varepsilon'_m = 2.3 \pm 3 \times 10^{-3}$ sec.$^{-1}$, $t'_0 = 72 \pm 2$ min. from insemination, $2r_0 = 58 \pm 1 \times 10^{-4}$ cm., $K = 4.5 \times 10^{-4}$ cm. sec.$^{-1}$, and $\gamma/\eta = 5 \times 10^{-4}$ cm. sec.$^{-1}$. The values of $2r_0$ could not be measured with much accuracy, because the cells were not sufficiently regular. The values used here were determined by extrapolating the curves, and are perhaps ten per cent too high. Comparing the values of the parameters of second cleavage with those of first cleavage, we find the values are almost identical, or not significantly different except for t'_0 and $2r_0$ which are necessarily different. The value for $2r_0$ for the half cells should be 0.8 that of the whole cell. A sample curve is shown in Figure 2*c*, where $A = .025$ sec.$^{-1}$, $B = .065$ sec.$^{-1}$, $t_0 = 72.2$ min., and $2r_0 = 58 \times 10^{-4}$ cm.

Discussion. In the early stages of the development of a theory, one does not expect too much agreement with experiment. When predictions can be made, they should be tested. If the prediction is verified by experiment, further development of the theory is suggested. If the prediction is not borne out, it is necessary to interpret the meaning of the failure on the basis of the theory, modify the theory, or suggest how other factors, which have not been considered may be responsible. It is essential that the order of magnitude of the parameters be in agreement with values obtained by substituting plausible values of the more basic constants of which they are made up. The expression of K is given in equation (1). As discussed previously (Landahl, 1942), the expression for K is more complex, but the order of magnitude is probably not much changed. If we take $\mu \sim 10^{-1}$, $M \sim 10^{2}$, $D_e \sim 5 \times 10^{-6}$, and $\eta \sim 10^{-1}$, then since $K \sim 5 \times 10^{-4}$, we find that it is sufficient that q be of the order of 10^{-9} gm. cm.$^{-3}$ sec.$^{-1}$. The parameter q is to be considered an effective rate of production, and thus may be of the order of, or less than the q values of the most rapid processes, those of respiration. This value is well below those

for respiration (Rashevsky, 1940, chap. ii). The value of K is thus found to be satisfactory. A possible increase in A and B, discussed in the preceding section, would thus be taken into account.

However, equation (2) predicts that, other things being constant, K should be proportional to the volume of the cell. It would seem, that for a half cell, the value of K should then be half that of the whole cell. This is not borne out here, but is for the case of constriction to be discussed subsequently.

The value of γ/η would be of the order of unity if we take $\gamma \sim 10^{-1}$ and $\eta \sim 10^{-1}$ as above. Comparing this with the values obtained, we find a factor of several thousand. It might be pointed out in this connection that this is just the factor obtained by E. N. Harvey and H. Shapiro (1941) between the "relaxation" times of cells deformed by squeezing and cells deformed by centrifuging. The value of γ for fertilized eggs without membranes could probably be considerably smaller than that estimated from unfertilized eggs. The value of the viscosity of dividing eggs is considerably higher than that of unfertilized eggs. Another possible explanation lies in the simplification of the expression for γ/η by assuming that $b = 0$, or that $2D_i << D_e$. It is readily shown that the effect of increasing b is to increase both K and γ/η roughly by the factor $1/(1 - b)$. But this alone is hardly sufficient. Another factor was mentioned in a preceding sub-section which allows an increase of perhaps ten. These factors taken together could account for the discrepancy.

An important factor not considered is that some of the parameters, especially q, probably vary with time due to the numerous changes which are taking place. The introduction of such an effect should also make it possible to predict the elongation curve beyond the point of maximum into the region in which shortening again takes place. It has been suggested by R. Williamson that a factor which should be taken into account in this connection is the disturbance of the diffusion fields of each cell by its neighbor. This could result in equilibrium shapes other than a sphere.

One might expect that γ/η would be larger for cells with membranes. This is found to be the case, the increase being by a factor of 4.3. However, K also was found to be larger, though not by quite as large a factor. This might be interpreted as implying that D_e is decreased, thus K increased, by the presence of the membrane, as the latter is essentially external to the cell.

Summary. We have seen that the shape of the experimental elongation curve is predicted fairly well by the theory, as illustrated by Figures 1 and 2. In the composite plot of values, as shown in Fig-

ure 1, the trend may deviate somewhat at the very beginning, producing a slight inflection. Aside from this, the entire positive part of the experimental curve of elongation rate with time is a parabola. The parameters of the elongation curves are given for various experimental conditions. The value of the parameter γ/η appears to be too small compared with the ratio of γ to η, estimated directly. Factors are discussed which can account for this apparent discrepancy. The parameter K is of an order of magnitude consistent with the expressions given by equation (2).

A COMPARISON OF THE CONSTRICTION EQUATION WITH EXPERIMENTAL DATA

An expression for the constriction rate for advanced stages was derived by G. Young (1939b). A more detailed treatment, though only approximate, was given by N. Rashevsky (1941) which indicated that the results first mentioned might hold for a large part of the constriction process. The expression is given by (Rashevsky, 1940, chap. iii)

$$r^2 = r'^2 - 2Qt\,, \tag{23}$$

where $2r$ is the width of the "neck", r' is an integration constant and

$$Q = Kr_0/88\,, \tag{24}$$

in which K is given by equation (2).

The extent to which the equation agrees with the data is illustrated in Figures 2*a*, 2*b*, and 2*c*. In some cases the curve remained essentially straight or showed an inflection in about the middle part of the curve. Where a curve was concave downward to beyond half constriction, that part of the curve was used if possible. A small number of curves could not be used, most of which were from the same batch of eggs. A few others were not used because the points were too scattered or too few.

For each of the curves used, the point of inflection was estimated. Three-fourths of the curves showed inflection points below $r = 26 \times 10^{-4}$ cm. One-half of the curved showed inflection points below $r = 20 \times 10^{-4}$ cm., and one-fourth below 13×10^{-4} cm. As one measured values of $2r$ below the inflection point it became increasingly uncertain as to whether the furrow width was being measured, especially in eggs in which the daughter cells tended to adhere.

The curves are not given beyond r_0 since the equation necessarily breaks down at some value $r < r_0$. For small widths, less than about 6×10^{-4} cm., measurements could not be made with accuracy from the

photographs. Furthermore, at about this stage one would expect secondary necking to begin. But the situation is complicated by the presence of strands from the spindle fibers connecting the daughter cells.

Eggs with membranes. Six eggs with membranes, two having been treated with KCN, were measured and the parameters r' and Q were obtained. The two KCN showed no significant difference from the others and were thus included to estimate the mean error. The average values obtained were: $r' = 1.3 \pm 1 \times 10^{-2}$ cm., $Q = 2.6 \pm 3 \times 10^{-8}$ cm.^{2} sec.$^{-1}$, so that from equation (24), $K = 6.2 \pm 7 \times 10^{-4}$ cm. sec.$^{-1}$. This value of K is somewhat less than one-half of the value obtained from the corresponding elongation curves.

Eggs with membranes removed by shaking. The same group of eggs with membranes removed by shaking were measured for the determination of r' and Q, giving the following average values: $r' = 1.3 \pm 1 \times 10^{-2}$ cm., $Q = 2.9 \pm 3 \times 10^{-8}$ cm.^{2} sec.$^{-1}$, from which $K = 7.3 \pm 8 \times 10^{-4}$ cm. sec.$^{-1}$. The value obtained for this group of eggs from the elongation curves is about forty per cent smaller than this value of K. The values of Q, r' and K are not significantly different in the eggs with and without membranes. An illustration of the constriction curve from an egg of this group is shown in Figure 2*a* where the parameters are $r' = 1.38 \times 10^{-2}$ cm. and $Q = 3.36 \times 10^{-8}$ cm.^{2} sec.$^{-1}$.

Eggs with membranes removed by KCl treatment. The two eggs with membranes removed by KCl gave the following values of the parameters: $r' = 1.4 \times 10^{-2}$ cm., $Q = 3.7 \times 10^{-8}$ cm.^{2} sec.$^{-1}$, $K = 8.9 \times 10^{-4}$ cm. sec.$^{-1}$, and $r' = 1.5 \times 10^{-2}$ cm., $Q = 4.2 \times 10^{-8}$ cm.^{2} sec.$^{-1}$, $K = 10.6 \times 10^{-4}$ cm. sec.$^{-1}$. Both these values of Q, and also K, are above almost all of the other values while the value of K from the elongation curves decreased. The significance of Q will be discussed subsequently. An illustrative curve from the second of these eggs is shown in Figure 2*b*.

Eggs with membranes removed by shaking and treated with KCN. From these eggs the average values of the parameters are: $r' = 1.4 \pm 1 \times 10^{-2}$ cm., $Q = 2.8 \pm 3 \times 10^{-8}$ cm.^{2} sec.$^{-1}$, $K = 7.2 \pm 8 \times 10^{-4}$ cm. sec.$^{-1}$. Comparing these values with those obtained from the eggs similarly treated but without KCN we find them to be the same, that is, the curves are essentially unchanged by the KCN treatment, although the time to division was increased by about twenty-five per cent. There was no significant change in K from the elongation curves due to KCN treatment.

Eggs with membranes removed by shaking, second cleavage. From the measurements of the constriction of the second cleavage eggs, the following parameters were obtained: $r' = 1.2 \pm 1 \times 10^{-2}$ cm., $Q = 1.5 \pm 2 \times 10^{-8}$ cm.^{2} sec.$^{-1}$, $K = 4.8 \pm 6 \times 10^{-4}$ cm. sec.$^{-1}$. Compar-

ing these values with those from the first cleavage we see that Q and K are significantly smaller here. The value of K from elongation did not show this change. From these comparisons we find that the constriction rates are very much the same except for the half eggs. This suggests that the size of the cell may play a role. But this is already predicted by the definition of Q and K. In Figure 2*c* is a sample curve from this group for which the parameters are $r' = 1.24 \times 10^{-2}$ cm. and $Q = 1.75 \times 10^{-8}$ cm.^{2} sec.$^{-1}$.

The relationship between Q and r_0. From equations (24) and (2) we expect that Q should vary with r_0^4. But from recent studies (Landahl, 1942), we would expect K to be proportional to r_0^2 instead of to r_0^3. Thus Q should be proportional to r_0^3. For this reason the values of Q from each of forty-six eggs were plotted with the initial radius r_0. The resulting graph is shown in Figure 3. The same sym-

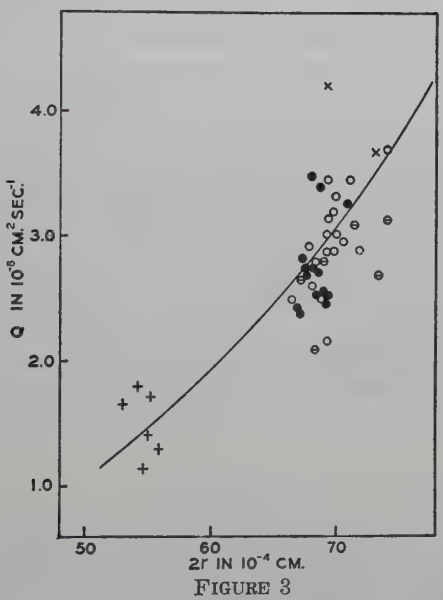

FIGURE 3

bols are used here as before, but in addition the values from half cells are designated by a plus sign. From the figure, one might suspect that the KCl eggs are different. In any case the correlation between Q and r_0, not including the half eggs or the KCl treated eggs is found to be 0.6 ± 1. This correlation is decreased by including the eggs treated with KCl. The curve of Figure 3, which has but one parameter, is given by $Q = 0.72 r_0^3$. Thus, this prediction is at least in part borne out. If one uses the fourth power relation given by (2) and (24), $Q = 220 r_0^4$, the agreement is poorer. The value of Q from sec-

ond cleavage was close to one-half that at first cleavage. The values of $2r_0$ for the half cells were difficult to estimate. They were about five per cent less than that which would be obtained by assuming that each daughter cell contained one-half the original volume. In the case of eggs treated with KCl, the measurements could be made more accurately. The volume of the daughter cells indicated a net loss of about one or two per cent in volume.

The parameter Q is roughly determined by the average slope of the constriction curve in the region of half constriction. If one uses this average to measure the constriction rate, one can say that there is probably a positive correlation between the rate of constriction and size.

Summary. It his been found that the constriction curves are predicted to a fair degree of approximation. From the analysis of the constriction curves it has been possible to predict the value of K independently of that from the elongation curves. In both cases the order of magnitude is the same, but the one set of values vary from about one-third to three times that of the other, without apparent correlation. Since the values of K from the constriction curves seem to vary with r_0 as predicted, whereas this is not so in the case of the elongation data, one would be inclined to accept the former values in any comparisons. If so, except for a possible slight effect of the KCl treatment, the only effect on K that is found is that of the size of the cell. The value of Q for the daughter cells is close to one-half of the value of Q from the original cell.

The author is indebted to Dr. N. Rashevsky for his many suggestions, and to Dr. R. Buchsbaum for his kindness in permitting the use of the photographs and records.

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TABLE OF PARAMETERS

Parameters	Normal	Shaken	*KCl*	*KCN*	Second Cleavage
			Elongation Curves		
A sec^{-1}	.025	.024	.020	.020	.025
B sec^{-1}	.22	.059	.031	.048	.071
ε_m	.12	.40	.64	.44	.35
ε'_m 10^{-3} sec^{-1}	.37	2.3	3.3	2.2	2.3
t'_0 min	48.	46.	43.	57.	72.
$2r_0$ 10^{-4} cm	74.	69.5	71.	68.	58.
K 10^{-3} cm sec^{-1}	1.7	.45	.26	.36	.45
γ/η 10^{-3} cm sec^{-1}	2.1	.49	.24	.39	.5
			Constriction Curves		
Q 10^{-8} cm^2 sec^{-1}	2.6	2.9	3.9	2.8	1.5
r' cm	.013	.013	.015	.014	.012
K 10^{-3} cm sec^{-1}	.62	.73	1.0	.72	.48

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

A FUNDAMENTAL FORM FOR THE DIFFERENTIAL EQUATION OF COLONIAL AND ORGANISM GROWTH[1]

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When total cell number is used as the basic parameter of growth, rational equations which describe colonial and organism growth under varying circumstances have been derived from a single differential form. These equations result from making specific, but reasonable assumptions about two additive factors, ϕ and θ which determine community growth. The first factor (ϕ) is assumed to arise from conditions within the growing cell itself, while the second factor (θ) arises from interactions between the growing cells of the community. If it is further assumed that the cells of a community are homogeneous with respect to density and volume, it has been shown that the mathematical expressions commonly used to describe growth data may be rationally derived from the general form.

In attempting to describe rationally how a cell colony or a multicellular organism changes in time (t), the crucial preliminary question is to decide upon a parameter of description, $\psi(t)$. The necessary attributes of this parameter are: (1) ψ must, as nearly as possible, depend only upon the activity of living cells. (2) ψ must be such that all other parameters can be unambiguously expressed in terms of ψ. In view of these requirements it is strange that most theoretical studies of community growth have chosen for ψ virtually every dependent variable except total cell number. (See, for example, Ludwig, 1929; Bertalanffy, 1934, 1938; Wetzel, 1937). It will be shown that the total cell number, N, can best satisfy the conditions on a growth parameter, and furthermore, that in terms of N all the important rational growth equations and two of the equations heretofore regarded as empirical can be shown to be but special cases of a fundamental differential form.

The phrase used above, "activity of living cells," is a vague term which veils much ignorance both about "living" and about "cells." It is not the place here to investigate the term. Let us only remark that

[1] Clerical assistance in the preparation of these materials was furnished by the personnel of Work Projects Administration, Official Project No. 65-1-08-62, Unit A-8.

within the limits of our knowledge a living system always exhibits the phenomena of metabolism and irritability. Under this definition not all the substance of a cell is living, since yolk stores, fat stores, or water stores, within a cell are no more "living" than the same substances outside the cell. Nevertheless as the absolute amounts of these substances in a cell change with time, the usual parameters, total mass, surface, and volume may also change. It is thus very clear that the parameters, mass, surface, and volume could not possible be expressions—except in a very indirect sense—of the phenomena we call living. Furthermore, indices of metabolism and irritability vary in time as a result of physiological processes not associated with growth, e.g., exercise, temperature changes, etc. On the other hand the process of cell division is unquestionably associated with living protoplasm in a most direct way, so that it must be concluded that the measure of cell division, namely cell number, is a basic parameter for a theoretical analysis of growth.

To derive the fundamental differential equation describing growth, consider a community, be it a colony or an organism, of N cells at time t. Let us postulate that two factors are responsible for changes in N as t increases: (1) a factor ϕ, which resides within the cells, and would be present were the cells infinitely removed from each other, and (2) a factor θ, affecting the cells because of interactions between cells. Assuming that these two effects are additive, we may write,

$$\frac{dN}{dt} = \phi + \theta. \tag{1}$$

(These are not stringent postulates; we only require that both cell and interaction contribute to the division of the cell, as of course they do.) Let us now consider ϕ and θ in turn. Assuming no interactions between cells, it is reasonable to suppose that at any one time the rate of cell number increase is proportional to the number of cells present. However, as time progresses the "constant" of proportionality will in general change; in other words the "constant" of proportionality should be a function of time. Such an assumption would lead to the general form of differential equation,

$$\frac{dN}{dt} = f_1(x_1, x_2, \cdots, x_n, t)$$

where the x's are physical parameters and t is time. This is indeed what we are about to write. While this equation is mathematically quite permissible, it obscures an important step in physical reasoning, namely, the way in which t is introduced into the right-hand

member. For the pointing out of this step, and for the following inclusion, we are grateful to N. Rashevsky. Physical functions are determined at any instant by the values of physical variables, and depend on time only insofar as the latter depend on time. Thus it may be that a parameter, x_i, changes in time,

$$\frac{dx_i}{dt} = f_2(r_1, r_2, \cdots, r_m)$$

whence,

$$x_i = f_3(x_{i_0}, t)$$

where x_{i_0} is the value of x_i at the zero point of time. Substituting in the equation for N, we are then able to replace x_i by x_{i_0}, t, and similarly for other parameters. The right hand member then becomes rigorously meaningful, with the zero point of time operationally defined, and can be evaluated for any given t.

Furthermore we shall later cite cases where the coefficient of N may depend upon N as well as t. Accordingly we have in general,

$$\phi = A(N, t) \cdot N. \qquad (2)$$

On the other hand, while the interaction effect must somehow depend upon the number of cells present, the dependence need not be linear, but rather upon N^k, where in the simplest case k is some constant. As before, the coefficient of proportionality is a function of N as well as of t. Thus.

$$\theta = B(N, t) \cdot N^k. \qquad (3)$$

Putting together (1) (2) and (3) we have

$$\frac{dN}{dt} = A(N, t) \cdot N + B(N, t) \cdot N^k. \qquad (4)$$

The fundamental character of equation (4) is demonstrated by the fact that by making reasonable assumptions about the functions A and B, many phenomena which affect growth can be incorporated into the form (4) without sacrificing its rationale.

The intrinsic factor ϕ. For instance, the phenomenon of the lag phase in bacterial and protozoan growth can reasonably be regarded as the approaching of the steady state initial to active proliferation. In the simplest case, the effect might be expressed by the well known transient function, $k\, e^{-\lambda t}$, in which case we would set

$$A = C_1 - C_2\, e^{-\lambda t} \qquad (C, \lambda, > 0).$$

Clearly as $t \to \infty$, $A \to C_1 =$ constant, but for t very small, i.e., during

the early stages of growth, A might be considerably below its eventual value, and λ correspondingly low.

The interaction factor θ. It is evident that θ will express the net effect of inhibitory and facilitative interactions. If these interaction effects are independent of one another, each will contribute an additive term to θ, and θ will be represented by a sum; if they are all related, θ could be a single product function. In the most general case, θ would be a sum of product functions, θ_i, where each θ_i is given by

$$\theta_i = B_i(N, t) \cdot N^{k_i} \tag{5}$$

and

$$\theta = \sum_i \theta_i .$$

As examples of negative or inhibitory interactions ($\theta_i < 0$) we might cite (1) the competition by cells for nutrient materials; (2) mechanical effects, e.g., compression; (3) spatial effects, such as the distortion of nutritive diffusion fields of a cell by its neighbors; (4) production of harmful metabolites. Consideration of positive interactions immediately brings to mind endocrine effects, e.g., "growth" hormone, thyroxine, etc. One way of treating these effects would be to consider a gland as a sub-community which does not exert its influence on the entire community until some time characteristic of the gland. The simplest mathematical formulation would then be

$$\theta_i = B_i \text{ (function of + only)} \cdot N_i^1,$$

where B must express the growth curve of the gland alone, and N_i the number of secreting cells in the *gland* (which are implicitly assumed functionally homogeneous). An alternative and simpler way is, however, suggested by the experimental fact that the most important case of hormonal influence, as, for example, puberty in mammals, occurs at the same time that $d^2N/dt^2 = 0$. It would thus be equally reasonable to set

$$B_i = f \frac{d^2N}{dt^2}$$

and therefore

$$\theta_i = N_i^1 f \frac{d^2N}{dt^2}.$$

This is an important case where B is a function of N as well as of t. The exponent k_i (5) may be chosen to conform with any particular hypothesis. Concrete illustrations will be presented below.

These examples suffice to show that under certain specific hypotheses we can express interactions quite rationally by the function (5),

and thus complete our justification for the use of the form (1). We will now study integrals of the form (1) under various rational assumptions regarding ϕ and θ.

Case I: Linear Proliferation; Universally Deleterious Metabolite Produced by all Cells at a Uniform Rate. If we assume that cells infinitely removed from each other have equal and constant division times, it is easy to show that,

$$\phi = AN, \tag{6}$$

where A is a true constant (no transient or lag effects). If now the cells are brought together and if each cell produces a substance which is harmful to every cell in the community including itself, and the proportionality constant is B, then the sum of harmful effects is BN^2. This follows because the total number of effects of N cells upon themselves is BN; Furthermore each cell acts upon $N-1$ others, and therefore the number of effects of cells upon their fellows is $BN(N-1)$. The total number of harmful effects is thus $BN + BN(N-1) = BN^2$, and we may set

$$\theta = -BN^2. \tag{7}$$

Combining (1), (6), and (7), we obtain

$$\frac{dN}{dt} = AN - BN^2 = BN\left(\frac{A}{B} - N\right). \tag{8}$$

If $B \equiv \beta$ and $A/B \equiv \alpha$, (8) integrates directly to

$$N = \frac{\alpha}{1 + Ke^{-\alpha\beta t}} \tag{9}$$

where K is a constant of integration.

Case II: Linear Proliferation; Universally Deleterious Metabolite Produced by all Cells at a Variable Rate. In addition to the hyptheses of Case I, let us postulate that the proportionality constant B changes in time as discussed earlier. We can attempt to describe this time variation by a power function of t, thus

$$B = \sum_{s=0}^{s=n} k_s t^s.$$

Substituing into (1) we obtain,

$$\frac{dN}{dt} = AN - N^2 \sum_{s=0}^{s=n} k_s t^s. \tag{10}$$

Equation (10) integrates to

$$N = \text{const.} + \frac{\alpha}{1 + me^{B}}. \tag{11}$$

Case III:*Constant Rate of Proliferation; Foodstuffs as Limiting Factor*: An interesting simple case is to consider the proliferation rate, ϕ, (1) a constant,

$$\phi = \alpha k \qquad (\alpha\,, k\,, \text{constants}).$$

(Here we have broken up the constant into two factors for algebraic convenience), and to assume that retardation is due to a shortage of foodstuffs. The latter effect can evidently be set proportional to the number of cells present, let us say,

$$\theta = -kN\,.$$

The rate equation,

$$\frac{dN}{dt} = \alpha k - kN\,, \tag{12}$$

this integrates to

$$N = \alpha(1 - e^{-kt}). \tag{13}$$

Case IV: *All Cells Produce A Stimulating Substance Which takes Effect According to Pharmacological Laws; Foodstuffs as Limiting Factor.* If all cells produce a growth stimulant, the amount of substance present at any time is proportional to the number of cells. The effect, however, need not be so; in fact it is common pharmacological experience that the effect of a dose is proportional to the *per cent* increase in the substance. (This general principle has much wider application than pharmacology; in physiology it has been formulated quantitatively by Weber and Fechner). Under those circumstances the effect of *unit* amount of substance would be proportional to the logarithm of the amount of substance, which in turn is proportional to the number of cells. The total effect is then proportional to the effect of unit amount and to the amount, in other words,

$$\phi = aN \log k_2 N$$

as before,

$$\theta = -\,\text{const.} \times N = -\,(a \log k_1)N\,.$$

Combining by (1),

$$\frac{dN}{dt} = aN \log k_2 N - (a \log k_1)N. \tag{14}$$

Equation (14) integrates to

$$N = \frac{k_1}{k_2} e^{ce^{at}}, \tag{15}$$

where c is a constant of integration.

These four examples we believe are sufficient to indicate the useful generality of the form (1), which in turn was based on the use of N as the essential parameter of growth. Before discussing them further we will consider the relation between the differential and integrated functions (8)-(15) and their analogues using mass, M, as the essential parameter. Let us begin by assuming that for the k-th cell the average density is $\bar{\rho}_k$ and the volume, v_k, so that its mass is

$$m_k = \bar{\rho}_k v_k \tag{16}$$

and obviously,

$$M = \sum_{k=1}^{k=N} \bar{\rho}_k v_k. \tag{17}$$

Since $M = f(N, t, \bar{\rho}_k, v_k)$ we may also write,

$$\frac{dM}{dt} = \frac{\partial M}{\partial N}\frac{dN}{dt} + \sum_{k=1}^{k=N} \frac{\partial M}{\partial \bar{\rho}_k}\frac{d\bar{\rho}_k}{dt} + \sum_{k=1}^{k=N} \frac{\partial M}{\partial v_k}\frac{dv_k}{dt}. \tag{18}$$

The set, (17) and (18), obviously give the desired relations. However, it will be observed that in practice an inescapable assumption to be made is that the cells among each other are homogeneous with respect to mass, density, and volume. (Although our differential form did not depend upon any such assumption, each of the specific hypotheses *I* to *IV* contained it.)

In that case (18) becomes simply

$$M = N\rho v. \tag{19}$$

Whence on substitution into (18) we have

$$\frac{dM}{dt} = \frac{M}{N}\frac{dN}{dt} + \frac{N}{\rho}\frac{d\rho}{dt} + \frac{N}{v}\frac{dv}{dt}. \tag{20}$$

If *in addition*, ρ and v are considered constant in time, (20) becomes simply $dM/dt = \text{const.} \times dN/dt$, and the four cases we have studied can be written in terms of *mass* and time, using the same contants referred to mass and time. The mass analogues of Equations (9), (11), (13) and (15) are thus;

$$M = \frac{\alpha}{1 + K_e^{-t}} \tag{21}$$

$$M = \text{const.} + \frac{\alpha}{1 + me^{B}} \tag{22}$$

$$M = \alpha(1 - e^{-kt}), \tag{23}$$

and

$$M = \frac{k_1}{k_2} e^{ce^{at}}, \tag{24}$$

which may be recognized respectively as the equations of T. B. Robertson (1926), R. Pearl (1925), Mitscherlich and others such as R. M. Jenss and N. Bayley (1939), and B. Gompertz (1825). The first two of these have heretofore been derived on the basis of chemical analogies which were admittedly fictitious while the last two have been up to now regarded as purely empirical (see A. J. Lotka (1925), S. Brody (1927), S. A. Courtis (1932) and I. Schmalhausen (1931).

In closing we may remark, perhaps unnecessarily, that there is a many-to-one correspondence between an integral form and a differential equation; so that interpretation of the constants in equations (21) to (24) is not unique, although the meanings ascribed to them in our derivations are certainly one possible set.

We are grateful to Professor S. F. Cook and Mr. F. Kreutzer for reading and criticizing the manuscript.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

A NOTE ON THE DIFFUSION OF ELECTROLYTES IN CELLS

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A somewhat simpler solution is given to the problem previously discussed by R. R. Williamson relating to the diffusion of a metabolized electrolyte whose ions have different mobilities.

R. R. Williamson (1939, 1941) has calculated the electrical forces that would be present in a cell metabolizing electrolytes, making certain simplifying assumptions and approximations. The purpose of this note is to introduce some substitutions which simplify the form of the result, and to correct an error in the second paper. In the first paper the problem considered is to determine the electrical forces under the assumption of differential transport rates for the two ions within the cell, but infinite permeabilities and external diffusion coefficients. Williamson's fundamental equations (9) whose solution gives the "average" internal concentrations of the two ions within the cell are derived from a pair (not numbered) which may be written

$$\begin{aligned} \rho\frac{D_+}{M_+}\bar{c}_+^{\,2} - \rho\frac{D_+}{M_-}\bar{c}_+\bar{c}_- + 6D_+\bar{c}_+ - r_0^2 q_+ - 6D_+c_{0+} &= 0, \\ \rho\frac{D_-}{M_-}\bar{c}_-^{\,2} - \rho\frac{D_-}{M_+}\bar{c}_+\bar{c}_- + 6D_-\bar{c}_- - r_0^2 q_- - 6D_-c_{0-} &= 0. \end{aligned} \tag{1}$$

The concentrations c are all given in gm cm^{-3}, and the productions q are in corresponding units. Evidently mol cm^{-3} is a preferable unit, especially since the molar production rates, and the external molar concentrations are equal. Moreover, the interest lies in the *difference* between the internal ionic concentrations, and this difference can be non-zero only so long as the production rate is non-null and the two diffusion coefficients are different. It is therefore appropriate to set

$$c_0 = \frac{c_{0+}}{M_+} = \frac{c_{0-}}{M_-}, \qquad q = \frac{q_+}{M_+} = \frac{q_-}{M_-}, \tag{2}$$

to obtain, after an obvious reduction,

$$\left(\frac{\bar{c}_+}{M_+}\right)^2 - \frac{\bar{c}_+}{M_+}\frac{\bar{c}_-}{M_-} + \frac{6}{\rho}\frac{\bar{c}_+}{M_+} - \frac{r_0^2}{D_+\rho}q - \frac{6}{\rho}c_0 = 0,$$
$$\left(\frac{\bar{c}_-}{M_-}\right)^2 - \frac{\bar{c}_-}{M_-}\frac{\bar{c}_+}{M_+} + \frac{6}{\rho}\frac{\bar{c}_-}{M_-} - \frac{r_0^2}{D_-\rho}q - \frac{6}{\rho}c_0 = 0. \tag{3}$$

Since for $D_+ = D_-$ we have $\bar{c}_+ : M_+ = \bar{c}_- : M_-$, the suggestion is immediate that we introduce parameters which vanish with the differences. We have, in fact, on adding and subtracting the equations, the equivalent pair

$$\left(\frac{\bar{c}_+}{M_+} - \frac{\bar{c}_-}{M_-}\right)\left(\frac{\bar{c}_+}{M_+} + \frac{\bar{c}_-}{M_-} + \frac{6}{\rho}\right) = \frac{r_0^2 q}{\rho}\left(\frac{1}{D_+} - \frac{1}{D_-}\right),$$
$$\left(\frac{\bar{c}_+}{M_+} - \frac{\bar{c}_-}{M_-}\right)^2 + \frac{6}{\rho}\left(\frac{\bar{c}_+}{M_+} + \frac{\bar{c}_-}{M_-}\right) = \frac{12}{\rho}c_0 + \frac{r_0^2 q}{\rho}\left(\frac{1}{D_+} + \frac{1}{D_-}\right). \tag{4}$$

If we set

$$x = \frac{\bar{c}_+}{M_+} - \frac{\bar{c}_-}{M_-}, \qquad y = \frac{\bar{c}_+}{M_+} + \frac{\bar{c}_-}{M_-},$$
$$\frac{u}{v} = \frac{6r_0^2 q}{\rho^2}\left(\frac{1}{D_+} - \frac{1}{D_-}\right), \qquad \frac{1}{v} = \frac{r^2{}_0 q}{\rho}\left(\frac{1}{D_+} + \frac{1}{D_-}\right) + \frac{12}{\rho}c_0 + \frac{36}{\rho^2}, \tag{5}$$

we have

$$x\left(y + \frac{6}{\rho}\right) = \frac{\rho}{6}\frac{u}{v},$$
$$x^2 + \frac{6}{\rho}\left(y + \frac{6}{\rho}\right) = \frac{1}{v}, \tag{6}$$

which, for small u, in fact for

$$u^2 < v - \frac{36}{\rho^2}v^2$$

can have but a single solution. We have thus

$$vx^3 - x + u = 0 \tag{7}$$

as a fairly simple cubic for determining the concentration difference for the two ions. Being already in "reduced" form, the closed solution is easily written. However, the expansion in powers of x contains only odd powers, and is given as follows:

$$x = u + vu^3 + 3v^2u^5 + \cdots. \tag{8}$$

For a cell with finite permeability (Williamson 1941), if we set

$$\xi = \frac{\pi r_0^2 N \varepsilon^2}{3KkT},$$

R. R. Williamson's equations (12)-(15) require correction and should be as follows:

$$\frac{Qr_0^2}{6D_+} = \bar{C}_+ - C_{1+} + \xi \bar{\Delta} \bar{C}_+, \tag{9}$$

$$\frac{Qr_0}{3h_+} = C_{1+} - C_0 + \xi \frac{\delta}{r_0} (\bar{\Delta} + \Delta_1)(C_{1+} + C_0), \tag{10}$$

$$\frac{Qr_0^2}{6D_-} = \bar{C}_- - C_{1-} - \xi \bar{\Delta} \bar{C}_-, \tag{11}$$

$$\frac{Qr_0}{3h_-} = C_{1-} - C_0 - \xi \frac{\delta}{r_0} (\bar{\Delta} + \Delta_1)(C_{1-} + C_0), \tag{12}$$

where now the C's and the Q are in terms of mols per cc. Then on adding (9) and (10), (11) and (12), and taking the sum and difference of the resulting equations we obtain the following equations:

$$Q\left(\frac{r_0^2}{6D_+} + \frac{r_0^2}{6D_-} + \frac{r_0}{3h_+} + \frac{r_0}{3h_-}\right) =$$

$$\bar{C}_+ + \bar{C}_- - 2C_0 + \xi \bar{\Delta}^2 + \xi \frac{\delta}{r_0} (\bar{\Delta} + \Delta_1)\Delta_1,$$

$$Q\left(\frac{r_0^2}{6D_+} - \frac{r_0^2}{6D_-} + \frac{r_0}{3h_+} - \frac{r_0}{3h_-}\right) =$$

$$\bar{\Delta} + \xi \bar{\Delta}(\bar{C}_+ + \bar{C}_-) + \xi \frac{\delta}{r_0} (\bar{\Delta} + \Delta_1)(\bar{C}_+ + \bar{C}_- + 2C_0).$$

If we introduce the following notation:

$$\lambda Q = Q\left[\frac{r_0^2}{6D_+} + \frac{r_0^2}{6D_-} + \frac{r_0}{3h_+} + \frac{r_0}{3h_-}\right],$$

$$\Lambda Q = Q\left[\frac{r_0^2}{6D_+} - \frac{r_0^2}{6D_-} + \frac{r_0}{3h_+} - \frac{r_0}{3h_-}\right],$$

$$x = \bar{\Delta}, \qquad x_1 = \Delta_1,$$

$$y = \bar{C}_+ + \bar{C}_-, \qquad y_1 = C_{1+} + C_{1-}, \tag{13}$$

$$\xi_1 = \xi\delta/r_0.$$

Our equations are

$$\lambda Q = y - 2C_0 + \xi x^2 + \xi_1 (x + x_1) x_1 , \tag{14}$$

$$\Lambda C = x + \xi xy + \xi_1 (x + x_1)(y + 2C_0) . \tag{15}$$

Since

$$\xi_1 = \xi \frac{\delta}{r_0} , \quad \frac{\delta}{r_0} \approx 10^{-3} ,$$

and

$$|(x + x_1) x_1| \approx x^2$$

usually;

$$\xi x^2 >> \xi_1 (x + x_1) x_1 , \quad \xi \approx 10^{12} ,$$

and our equations are very closely approximated by

$$\lambda Q = y - 2C_0 + \xi x^2 , \tag{16}$$

$$\Lambda Q = x + \xi xy . \tag{17}$$

From (16)

$$y = \lambda Q + 2C_0 - \xi x^2 , \tag{18}$$

and substituting in (17),

$$\Lambda Q = x + \xi x [\lambda Q + 2C_0 - \xi x^2] ,$$

or, after rearranging,

$$\frac{\xi^2 x^3}{1 + \xi (\lambda Q + 2C_0)} - x + \frac{\Lambda Q}{1 + \xi (\lambda Q + 2C_0)} = 0 .$$

If then we let

$$v_1 = \frac{\xi^2}{1 + \xi (\lambda Q + 2C_0)} , \quad u_1 = \frac{\Lambda Q}{1 + \xi (\lambda Q + 2C_0)} ,$$

the equation has the form of (7) and the expansion (8) is the same when subscripts are placed on the u and v. The expression for y is then obtained by substitution into (18).

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

PERIODIC PHENOMENA IN THE INTERACTION OF TWO NEURONS

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The periodic and resonant properties of a closed neuron circuit are exhibited and applications to some visual and electrophysiological phenomena are discussed.

Various properties of closed neuron circuits have been discussed previously. In particular, Landahl and Householder (1939) discussed the conditions for periodicities in the self-exciting neuron.

In the circuit to be considered, neuron *I*, producing excitatory substance ε only, synapses with *II*, which produces inhibitory substance j only, and *II* in turn synapses with *I*. External stimulation of amounts E_1 and E_2 may be introduced through fibers *I'* and *II'* at synapses (1, 2) and (2, 1) respectively.

We consider the equations

$$\begin{aligned} \frac{d\varepsilon}{dt} &= \beta_1(E_2 - j - h_1) - \alpha_1\varepsilon \ , \\ \frac{dj}{dt} &= \beta_2(E_1 + \varepsilon - h_2) - \alpha_2 j \ , \end{aligned} \tag{1}$$

where α_i and β_i are reaction constants having positive values and E_i are arbitrary functions of time. The auxiliary equation for this system has the roots

$$m = -\frac{\alpha_1 + \alpha_2}{2} \pm \sqrt{\left(\frac{\alpha_1 + \alpha_2}{2}\right)^2 - \alpha_1\alpha_2 - \beta_1\beta_2} \ . \tag{2}$$

The behavior of the system will be periodic provided

$$\left(\frac{\alpha_1 + \alpha_2}{2}\right)^2 - \alpha_1\alpha_2 - \beta_1\beta_2 < 0 \ . \tag{3}$$

It will henceforth be assumed that this condition is satisfied.

We will adopt the notations

$$\begin{aligned} \alpha_1 + \alpha_2 &= 2p \,, \\ \alpha_1\alpha_2 + \beta_1\beta_2 &= g \,, \\ p^2 - g &= -q^2 \,. \end{aligned} \tag{4}$$

The complementary functions may then be written

$$\begin{aligned} \varepsilon_c &= e^{-pt}(c_1 e^{iqt} + c_2 e^{-iqt}) \,, \\ j_c &= e^{-pt}(c'_1 e^{iqt} + c'_2 e^{-iqt}) \,, \end{aligned} \tag{5}$$

or, by using trigonometric functions, as

$$\begin{aligned} \varepsilon_c &= e^{-pt}(A \cos qt + B \sin qt) \,, \\ j_c &= e^{-pt}(A' \cos qt + B' \sin qt) \,. \end{aligned} \tag{6}$$

The constants A' and B' are not independent of A and B, but satisfy the relations,

$$\begin{aligned} A' &= \left[\frac{\alpha_2 - \alpha_1}{2} A - qB\right] \Big/ \beta_1 \,, \\ B' &= \left[qA + \frac{\alpha_2 - \alpha_1}{2} B\right] \Big/ \beta_1 \,. \end{aligned} \tag{7}$$

Making these substitutions and rewriting, we have

$$\begin{aligned} \varepsilon_c &= e^{-pt}\,\gamma \sin\,(qt + \phi) \\ j_c &= e^{-pt} \sqrt{\frac{\beta_2}{\beta_1}}\,\gamma \sin\,(qt + \phi + \delta) \end{aligned} \tag{8}$$

where γ and ϕ are the constants of integration and δ is given by

$$\sin\delta = -\frac{q}{\sqrt{\beta_1\beta_2}}, \quad \cos\delta = \frac{\alpha_2 - \alpha_1}{2\sqrt{\beta_1\beta_2}}. \tag{9}$$

In the case that the imposed stimulations, E_1 and E_2, are constant, the particular integrals for ε and j are given by

$$\begin{aligned} \varepsilon_\infty &= \beta_1[\alpha_2(E_2 - h_1) - \beta_2(E_1 - h_2)]/g \,, \\ j_\infty &= \beta_2[\alpha_1(E_1 - h_2) + \beta_1(E_2 - h_1)]/g \,. \end{aligned} \tag{10}$$

The complete solutions for constant E_1 and E_2 are then

$$\begin{aligned} \varepsilon &= e^{-pt}\,\gamma \sin(qt + \phi) + \varepsilon_\infty \\ j &= e^{-pt} \sqrt{\frac{\beta_2}{\beta_1}}\,\gamma \sin(qt + \phi + \delta) + j_\infty. \end{aligned} \tag{11}$$

Since ε and j must be always positive we must satisfy the conditions

$$\varepsilon_\infty > 0\,, \qquad j_\infty > 0\,. \tag{12}$$

This is equivalent to saying that in the E_1, E_2 plane, the point (E_1, E_2) lies above both of a certain pair of lines

$$\begin{aligned} \alpha_2(E_2 - h_1) - \beta_2(E_1 - h_2) &= 0\,, \\ \beta_1(E_2 - h_1) + \alpha_1(E_1 - h_2) &= 0\,. \end{aligned} \tag{13}$$

We see that we must have

$$\begin{aligned} &E_2 > h_1\,, \\ &\frac{\alpha_2}{\beta_2} > \frac{E_1 - h_2}{E_2 - h_1} > -\frac{\beta_1}{\alpha_1}. \end{aligned} \tag{14}$$

In evaluating γ and ϕ we will assume that at $t_0 = 0$,

$$E_2 - h_1 - j_0 \geqq 0\,, \qquad E_1 - h_2 + \varepsilon_0 \geqq 0\,, \tag{15}$$

with E_1 and E_2 satisfying conditions (14). Evaluating ε using these restrictions, we obtain

$$\varepsilon_0 = \gamma \sin\phi + \varepsilon_\infty\,, \tag{16}$$

$$\left.\frac{d\varepsilon}{dt}\right|_{t=0} = \beta_1(E_2 - h_1 - j_0) - \alpha_1\varepsilon_0 = q\,\gamma\cos\phi - p\,\gamma\sin\phi. \tag{17}$$

Then

$$\tan\phi = \frac{q(\varepsilon_0 - \varepsilon_\infty)}{\beta_1(E_2 - h_1 - j_0) - \alpha_1\varepsilon_0 - p(\varepsilon_0 - \varepsilon_\infty)}, \tag{18}$$

$$\gamma = \frac{1}{q}\left\{[\beta_1(E_2 - h_1 - j_0) - \alpha_1\varepsilon_0 + p(\varepsilon_0 - \varepsilon_\infty)]^2 + q^2(\varepsilon_0 - \varepsilon_\infty)^2\right\}^{\frac{1}{2}}. \tag{19}$$

In order for the function $\varepsilon(t)$ to be continuous for all positive values of t we must have $\varepsilon \geqq 0$ when $d\varepsilon/dt = 0$ and $d^2\varepsilon/dt^2 > 0$, or

$$\varepsilon_\infty + e^{-pt_1}\gamma\sin(qt_1 + \phi) > 0\,, \tag{20}$$

where t_1 is the time from $t = 0$ to the first minimum of ε. We evaluate t_1 by setting the time derivative of ε equal to zero and find

$$t_1 = \frac{1}{q}\left[\sin^{-1}\left(\frac{-q}{\sqrt{g}}\right) - \phi\right]. \tag{21}$$

Corresponding conditions are obtained from the requirement that $j \geqq 0$ at its first minimum.

The case of sinusoidal applied stimulation.

We will consider the case in which

$$\begin{aligned} E_2(t) &= E_0 \sin \theta t + E_2 \\ E_1(t) &= \mu E_0 \sin \theta t + \mu E_2 . \end{aligned} \tag{22}$$

For a particular integral of (1) we choose

$$V = c_1 \sin (\theta t + \omega) + c_2 \cos (\theta t + \omega) + c_3 . \tag{23}$$

Equating coefficients, we find

$$\begin{aligned} c_1 &= \frac{(\theta^2 - g) K E_0}{(\theta^2 - g)^2 + 4p^2\theta^2} , \\ c_2 &= -\frac{2p\theta K E_0}{(\theta^2 - g)^2 + 4p^2\theta^2} , \\ c_3 &= \beta_1[(\alpha_2 - \beta_2\mu) E_2 - \alpha_2 h_1 + \beta_2 h_2]/g = \varepsilon_\infty , \end{aligned} \tag{24}$$

where

$$K^2 = \beta_1^2[(\alpha_2 - \beta_2\mu)^2 + \beta_1^2\theta^2 , \tag{25}$$

and p and g are given by (4) above.

The particular integral for ε becomes

$$\varepsilon_p = \frac{E_0}{\rho} \sin (\theta t + \omega + \lambda) + \varepsilon_\infty , \tag{26}$$

where

$$\rho = \frac{1}{\beta_1} \sqrt{\frac{\theta^2}{\theta^2 + r^2}\left[4p^2 + (\theta - \frac{g}{\theta})^2\right]} , \tag{27}$$

with

$$r = \alpha_2 - \beta_2\mu . \tag{28}$$

The maxima and minima of $\rho(\theta)$ are found by setting $d\rho/d\theta = 0$ and solving for θ. This gives

$$\theta^2 = -r^2 \pm \sqrt{(r^2 - p^2 + q^2)^2 + 4p^2q^2} , \qquad \theta = 0, \tag{29}$$

for the extreme values of $\rho(\theta)$.

The amplitude at $\theta = 0$ is given by

$$\frac{E_0}{\rho_0} = \beta_1 r E_0/g . \tag{30}$$

For very large θ, $1/\rho$, and hence the amplitude, approaches zero.

Discussion.

To recapitulate, the above formulation shows that when a closed circuit consisting of one excitatory and one inhibitory neuron is subjected to appropriate constant stimulation an oscillatory response is set up having a period characteristic of the circuit, the oscillations diminishing toward a steady value characteristic of the stimulus. It is also shown that when a sinusoidally varied stimulus is applied the circuit responds synchronously, the amplitude of response being determined by the frequency of the imposed stimulation. The frequency to which the circuit responds maximally is known as the resonance frequency, and is related to the natural frequency of response to steady stimulation.

There are many instances of animal behavior under natural and experimental conditions which have the properties described. In some cases there is evidence that the above described mechanism cannot be considered as operative, at least exclusively. Of these we may mention the rhythmic potentials recorded from the brain, which have been shown by Libet and Gerard (1938) and others to depend on other factors than anatomical relationships of neurons. Such mechanisms as the scratch reflex and various cases of oscillatory (clonic) response to a steady stimulus would conform to the scheme presented above, with the proprioceptors, especially stretch receptors, corresponding to the inhibitory element and the motor nerve corresponding to the excitatory element. The above formulation would be adequate only within such an intensity range that the linear assumptions could be considered to hold.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

A THEORY OF ELECTRICAL POLARITY IN CELLS

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In general, there exist electrical potential differences along the axis of a spherical cell containing an asymmetric diffusion field. The electrical potential is calculated for any point on the axis of such a cell, which is assumed to contain metabolite ions and charged colloidal particles.

Consider a spherical cell of radius r_0, with its center at the origin. We shall assume that an existing metabolic polarity (Rashevsky, 1940) makes the concentration gradients greatest along the x-axis, and treat the cell by halves: the first half is the hemisphere whose axis is the positive x-axis, while the second half is the hemisphere whose axis is the negative x-axis. Our problem will be to determine, approximately, the electrical potential at a point P on the x-axis where $x = \alpha r_0$, if $-1 \leqq \alpha \leqq +1$. Thus we shall be able to determine the potential difference between any two points on the x-axis.

We shall deal with + and − ions which are being produced or consumed in the cell, and with catalyst colloidal particles which are assumed to be present in the cell. For simplicity we assume the permeability of the cell wall to the ions is ∞, and the external diffusion coefficients are also ∞.

$c_{i\pm}$ = average concentration of ion in moles cm^{-3} in the i-th half cell
Q_i = average rate of production of ion in moles cm^{-3} sec^{-1} in the *colloidal* charge in the i-th half cell
$D_\pm$ = internal diffusion coefficient of ion in cm^2 sec^{-1}
$\bar{\Delta}_i$ = average difference in concentration of ions of opposite signs in moles cm^{-3} in i-th half-cell
$B_\pm$ = mobility of ion $= D_\pm/kT$
k = Boltzmann constant
T = absolute temperature
$J_\pm$ = transport of ion in moles cm^{-2} sec^{-1}
f_{i+} = electric force on a + ion in i-th half cell ($f_{i+} = -f_{i-}$)

$F_i = \dfrac{f_{i+}\, r_0}{kT}$

V'_i = electrostatic potential in the first half cell resulting from the metabolite which is in the i-th half cell

V''_i = electrostatic potential in the second half cell resulting from the metabolite which is in the i-th half cell

n_i = number density of charged colloidal particles, inhibiting Q in the i-th half cell

$n = \dfrac{n_1 + n_2}{2}$

ν = number of excess + charges in units of one electronic charge, on a catalyst particle

ε = charge on an electron = 4.8×10^{-10} E.S.U.

$\delta_i = n_i \nu \varepsilon$ = charge density in i-th half resulting from charge on colloid

ϕ'_i = electrostatic potential in the first half cell resulting from the *colloidal* charge in the i-th half cell

ϕ''_i = electrostatic potential in the second half cell resulting from the *colloidal* charge in the i-th half cell

$\psi'_i = V'_i + \phi'_i$ = total electrostatic potential in the first half cell due to the charge in the i-th half cell

$\psi''_i = V''_i + \phi''_i$ = total electrostatic potential in the second half cell due to the charge in the i-th half cell

N = Avogadro's number

$R = +\sqrt{y^2 + z^2}$

ρ = charge density

Our steady-state diffusion equations become (Rashevsky, 1940; Williamson, 1939, 1941)

$$\begin{aligned}
\frac{2r_0^2 Q_1}{3D_+} &= (5 + F_1)C_{1+} - C_{2+} - 4C_0 \\
\frac{2r_0^2 Q_1}{3D_-} &= (5 - F_1)C_{1-} - C_{2-} - 4C_0 \\
\frac{2r_0^2 Q_2}{3D_+} &= (5 + F_2)C_{2+} - C_{1+} - 4C_0 \\
\frac{2r_0^2 Q_2}{3D_-} &= (5 - F_2)C_{2-} - C_{1-} - 4C_0
\end{aligned} \qquad (1)$$

If we can determine F_1 and F_2, we can solve these four equations for the four unknowns, C_{1+}, C_{1-}, C_{2+}, C_{2-}. A knowledge of these, plus

a knowledge of the quantities δ_i resulting from the distribution of charged colloidal particles, will enable us to calculate the approximate electrical potential as a point function, in particular, at the point $P(x = \alpha r_0 , y = 0 , z = 0)$

$$\psi = \int_\tau \frac{\rho d\tau}{Kr}$$

where τ is the volume of the cell and K is the dielectric constant

$$\begin{aligned} \rho &= N\varepsilon\bar{\Delta}_1 + \delta_1 \qquad \text{if } x > 0 \\ &= N\varepsilon\bar{\Delta}_2 + \delta_2 \qquad \text{if } x < 0 \\ d\tau &= 2\pi RdRdx \\ r &= \text{distance from } d\tau \text{ to } P \\ r^2 &= R^2 + (\alpha r_0 - x)^2 . \end{aligned}$$

Then

$$\psi'_1 = \frac{2\pi(N\varepsilon\bar{\Delta}_1 + \delta_1)}{K} \int_0^{r_0} dx \int^{\sqrt{r_0^2 - x^2}} \frac{RdR}{\sqrt{R^2 + (\alpha r_0 - x)^2}} .$$

Assuming $\alpha > 0$, we find

$$\psi'_1 = \frac{2\pi r_0^2(N\varepsilon\bar{\Delta}_1 + \delta_1)}{3K\alpha} \left[-2\alpha^3 \frac{3\alpha}{2} - 1 + (\alpha^2 + 1)^{3/2} \right] ,$$

$$\psi'_2 = \frac{2\pi r_0^2(N\varepsilon\bar{\Delta}_2 + \delta_2)}{3\alpha K} \left[\alpha^3 + \frac{3\alpha}{2} + 1 - (1 + \alpha^2)^{3/2} \right] .$$

$$\begin{aligned} \psi'(\alpha r_0) &= \psi'_1 + \psi'_2 \\ &= \frac{2\pi r_0^2}{3K\alpha} \left\{ (N\varepsilon\bar{\Delta}_2 + \delta_2) \left[\alpha^3 + \frac{3\alpha}{2} + 1 - (1 + \alpha^2)^{3/2} \right] \right. \\ &\quad \left. - (N\varepsilon\bar{\Delta}_1 + \delta_1) \left[2\alpha^3 - \frac{3\alpha}{2} + 1 - (1 + \alpha^2)^{3/2} \right] \right\} . \end{aligned} \tag{2}$$

$$F_1 = -\frac{r_0 \nu\varepsilon}{kT} \frac{d\psi'}{d(\alpha r_0)} = -\frac{\nu\varepsilon}{kT} \frac{d\psi'}{d\alpha} , \tag{3}$$

$$\begin{aligned} F_1 = -\frac{2\pi r_0^2 \nu\varepsilon}{3KkT} &\left\{ (N\varepsilon\bar{\Delta}_2 + \delta_2) \left[2\alpha + \frac{(1 - 2\alpha^2)(1 + \alpha^2)^{\frac{1}{2}} - 1}{\alpha^2} \right] \right. \\ &\left. - (N\varepsilon\bar{\Delta}_1 + \delta_1) \left[4\alpha + \frac{(1 - 2\alpha^2)(1 + \alpha^2)^{\frac{1}{2}} - 1}{\alpha^2} \right] \right\} . \end{aligned} \tag{4}$$

Since in performing our integration we assumed $\alpha > 0$ the foregoing computations apply only to the first half of the cell. The results may be applied to the other half of the cell, however, if we exchange $N\varepsilon\bar{\Delta}_1 + \delta_1$ and $N\varepsilon\bar{\Delta}_2 + \delta_2$. Hence for any two points on the x-axis equidistant from the origin (one in each half) defined by $x = \pm \alpha r_0$

$$\psi'(\alpha r_0) - \psi''(\alpha r_0)$$
$$= \frac{2\pi r_0^2}{3K\alpha}\left[(N\varepsilon\bar{\Delta}_1 + \delta_1) - (N\varepsilon\bar{\Delta}_2 + \delta_2)\right]\left[2(1+\alpha^2)^{3/2} - 3\alpha^3 - 2\right]. \quad (5)$$

$$F_2 = -\frac{2\pi r_0^2 \varepsilon \nu}{3KkT}\left\{(N\varepsilon\bar{\Delta}_1 + \delta_1)\left[2\alpha + \frac{(1-2\alpha^2)(1+\alpha^2)^{\frac{1}{2}} - 1}{\alpha_2}\right]\right.$$
$$\left. - (N\varepsilon\bar{\Delta}_2 + \delta_2)\left[4\alpha + \frac{(1-2\alpha^2)(1+\alpha^2)^{\frac{1}{2}} - 1}{\alpha_2}\right]\right\} \quad (6)$$

F_1 and F_2, expressed as the difference of two small quantities, in themselves small differences, will be much less than 5 in absolute value. Hence, if we let

$$\zeta = \frac{r_0^2}{9}\left(\frac{1}{D_+} + \frac{1}{D_-}\right),$$
$$\xi = \frac{r_0^2}{9}\left(\frac{1}{D_+} + \frac{1}{D_-}\right);$$

and neglect F in (1) we have

$$\bar{C}_{1+} + \bar{C}_{1-} - \bar{C}_{2+} - \bar{C}_{2-} = \bar{C}_1 - \bar{C}_2 = \zeta(Q_1 - Q_2) \quad (7)$$

and

$$\bar{\Delta}_1 = \bar{C}_{1+} - \bar{C}_{1-} = \frac{6Q_1}{5}\xi + \frac{\bar{\Delta}_2}{5},$$

$$\bar{\Delta}_2 = \frac{6Q_2}{5}\xi + \frac{\bar{\Delta}_1}{5},$$

or

$$\bar{\Delta}_1 - \bar{\Delta}_2 = \xi(Q_1 - Q_2). \quad (8)$$

Now let us assume that all the colloidal particles are positively charged. Then, treating them as a gas in a field of force derived from a potential, the distribution of the particles will be

$$\frac{n_1}{n_2} = e^{-\gamma(\bar{C}_1 - \bar{C}_2) - \frac{\nu\varepsilon}{kT}\left[\psi'\left(\frac{r_0}{2}\right) - \psi''\left(-\frac{r_0}{2}\right)\right]} \quad (9)$$

where $\gamma = 3Nv/2$, v being the volume of a colloidal particle.
Let

$$y = n_1 - n_2$$

$$Q_1 = Q_0 - an_1$$

$$Q_2 = Q_0 - an_2,$$

where a is a constant. Subtracting the last pair

$$Q_1 - Q_2 = -a(n_1 - n_2).$$

If we remember that $\delta_1 = n_1 \nu\varepsilon$ we can obtain the exponent of (9) as a constant times y

$$-\gamma(\dot{C}_1 - \dot{C}_2) - \frac{\nu\varepsilon}{kT}\left[\psi'(r_0/2) - \psi''(-r_0/2)\right]$$

$$= \left\{\gamma\zeta a + \frac{\pi r_0^2 \nu\varepsilon}{6KkT}\left[N\varepsilon\xi a - \nu\varepsilon\right]\cdot(10\sqrt{5} - 19)\right\}(n_1 - n_2)$$

or

$$\frac{n_1}{n_2} = e^{My}$$

where

$$M = \left[\gamma\zeta a + \frac{\beta}{kT}\left(\xi a - \frac{\nu\varepsilon}{N}\right)\right] \qquad (10)$$

$$\beta = \frac{\pi r_0^2 N \nu\varepsilon^2}{\varepsilon K}(10\sqrt{5} - 19) \qquad p = 10\sqrt{5} - 19.$$

By the same argument as that in N. Rashevsky, 1940, we find

$$y = 2n \tanh \frac{My}{2}. \qquad (11)$$

A stable distribution of colloidal particles is possible if equation (14) has a real positive root. If that root exists and if My is very small, we may expand $\tanh My/2$ and keep only the lowest powers.
We get

$$y = ynM\left(1 - \frac{M^2y^2}{12}\right)$$

whose roots $\neq 0$ are

$$y = \pm\frac{2}{M}\sqrt{\frac{3(nM-1)}{nM}} = n_1 - n_2 \qquad (12)$$

assuming $nM > 1$.

We have now obtained all the equations necessary to a solution of the problem, and we can predict the magnitude of the polarity and electrostatic potentials. In a subsequent paper, we will discuss the conditions for polarity, the kinds of polarity that can result from this mechanism, changes of polar state of a cell, and orders of magnitude of the electric potential differences at the poles.

The authors wish to acknowledge their indebtedness to Dr. N. Rashevsky and Dr. A. S. Householder for their frequent and helpful criticisms and suggestions.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

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MF:10

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

AN ALTERNATE APPROACH TO THE MATHEMATICAL BIOPHYSICS OF PERCEPTION OF COMBINATIONS OF MUSICAL TONES

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In connection with a previous paper on the same subject this different approach to the problem is outlined, which also leads to an expression for pleasantness values of different binary combinations of musical sounds.

In a previous paper (Rashevsky, 1942) we have treated the present problem under the assumption that the intensity of excitation of the centers corresponding to overlapping harmonics was the same as for centers corresponding to non-overlapping ones. We shall treat here the problem under a somewhat more general assumption. We shall consider the intensities of excitation of the centers corresponding to the non-overlapping harmonics as the same, while for a center corresponding to two overlapping harmonics, we shall take the excitation to be twice as great.

The total intensity of excitation of n' mutually inhibiting centers, excited with different intensities e_i, is (Rashevsky, 1942a) using the same notations as before

$$E = [1 - (n' - 1)b] \sum n'_i e_i , \tag{1}$$

where n_i is the number of centers with the intensity of excitation e_i. We have in general

$$\sum n'_i = n'. \tag{2}$$

In our particular case we have

$$e_1 = 2 , \quad e_2 = 1 , \quad n'_1 + n'_2 = n'. \tag{3}$$

Hence equation (1) becomes

$$E = [1 - (n' - 1)b] (2n'_1 + n'_2). \tag{4}$$

Introducing as in *loc. cit.* the quantity x, we have:

$$n' = xn; \quad n = n'/x = n'p/(2p-1);$$
$$n'_1 = n/p = n'/(2p-1); \tag{5}$$
$$n'_2 = n' - n'/(2p-1) = n'(2p-2)/(2p-1).$$

Hence

$$2n'_1 + n'_2 = 2n'/x. \tag{6}$$

Therefore, neglecting 1 as compared with n', and putting $n' = xn$, $bn = B$, we have

$$E = 2n(1 - Bx). \tag{7}$$

E decreases monotonically with x. Since experimentally it is known that the pleasantness rating has a maximum for approximately $x = 1{\cdot}8$ (Rashevsky, 1942), therefore we cannot in this case identify E directly with that pleasantness rating. We may consider however, that the pleasantness rating is determined by the excitation intensity of a higher center, which is connected with the center at which the excitation is E, by means of neurons having the characteristics:

$$A > B; \quad a > b; \quad \frac{A}{a} = \frac{B}{b}, \tag{8}$$

and for which E serves as a stimulus. For such a neuron in a steady state the intensity of excitation E^* will have a maximum for a certain value of E (Rashevsky, 1938). By a proper choice of the parameters involved in (7) and (8) we may obtain approximately the desired rank order of pleasantness. The difficulty with the octave, found in *loc. cit.* vanishes in this treatment. The octave will have a higher rating than the fifth, because for the octave $x = 1{\cdot}5$, as against 1·67 for the fifth.

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CONSERVATION OF SCHOLARLY JOURNALS

AN ANNOUNCEMENT

The American Library Association created this last year the Committee on Aid to Libraries in War Areas, headed by John R. Russell, the Librarian of the University of Rochester. The Committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after the first World War was that of completing foreign institutional sets of American scholarly, scientific, and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the Committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. As far as possible they will be completed from a stock of periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the cooperation of subscribers to this journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project or concerning the value of particular periodicals to the project should be directed to Wayne M. Hartwell, Executive Assistant to the Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.

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1. The Bulletin is devoted to publications of research in Mathematical Biophysics, as contributing to the physicomathematical foundations of biology in their most general scope.

2. Papers published in the Bulletin cover physicomathematical theories as well as any other mathematical treatments of biological phenomena, with the exception of purely statistical studies.

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5. Outside of the scope of the journal are papers of purely statistical nature or papers concerned only with empirical equations.

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All manuscripts should be typewritten double space. Equations should be numbered on the right consecutively. *Do not* use such notations as "equation 2a" or, "equation 5′ " etc. References should be all given at the end of the paper, arranged in alphabetic order by authors and for each author chronologically, following *exactly* the style used in the Bulletin. In text, reference should be made by giving in parentheses the name of the author followed by the year of publication. In case of several publications by the same author in the same year, use notations "1940a", "1940b", etc.

In writing equations, slanted lines should be used wherever possible.

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